REMARKS

Claims 4-8 and 11-17 are presented for examination. The specification and claims have not been amended. Applicants respond below to the remaining rejections raised by the Examiner in the final Office Action mailed on May 16, 2005.

Rejection under 35 U.S.C. §101 - Utility

The Examiner has maintained the rejection of Claims 4-8 and 12-13 for the reasons of record in paper number 105. The Examiner argues that there is no utility for the claimed polypeptides, and that a "utility of being a diagnostic target for melanoma or esophageal tumors is a utility that requires or constitutes carrying out further research to identify or reasonably confirm a 'real world' context of use." The specific arguments raised by the Examiner are addressed below.

Utility – Legal Standard

Applicants remind the Examiner of the proper legal standard for utility. According to the Utility Examination Guidelines ("Utility Guidelines"), 66 Fed. Reg. 1092 (2001), an invention complies with the utility requirement of 35 U.S.C. § 101, if it has at least one asserted "specific, substantial, and credible utility" or a "well-established utility." The Guidelines for Examination of Applications for Compliance With the Utility Requirement, set forth in M.P.E.P. § 2107 II(B)(1) gives the following instruction to patent examiners: "If the applicant has asserted that the claimed invention is useful for any particular practical purpose ... and the assertion would be considered credible by a person of ordinary skill in the art, do not impose a rejection based on lack of utility."

Also, as Applicants have previously established, the legal standard for demonstrating utility is a relatively low hurdle. An Applicant need only provide evidence such that it is **more likely than not that a person of skill in the art would be convinced, to a reasonable probability, that the asserted utility is true**. The evidence need not be direct evidence, so long as there is a reasonable correlation between the evidence and the asserted utility. **The standard is not absolute certainty.**

Here, the utility requirement under § 101 is satisfied because: (1) Applicants have provided reliable evidence that mRNA for the PRO3566 polypeptide is more highly expressed in

normal skin and esophageal tumor tissue compared to melanoma tumor and normal esophagus tissue, respectively; (2) Applicants assert that it is well-established in the art that a change in the level of mRNA for a particular protein, *e.g.* a decrease, generally leads to a corresponding change in the level of the encoded protein, *e.g.* a decrease; and (3) Given Applicants' evidence that the level of mRNA for the PRO3566 polypeptide is decreased in melanoma tumor and normal esophagus tissue, compared to normal skin and esophageal tumor tissue, respectively, it is likely that the PRO3566 polypeptide is differentially expressed in melanoma and esophageal tumors, and therefore, PRO3566 polypeptides are useful as diagnostic tools to distinguish tumor from normal tissue. The claimed polypeptides thus have utility as diagnostic tools for cancer.

Furthermore, Applicants have established that it is more likely than not that a person of skill in the art would be convinced, to a reasonable probability, that the asserted utility is true. Again, the standard for establishing an asserted utility is not statistical or absolute certainty.

The specific arguments raised by the Examiner in the Office Action regarding substantial utility are addressed below.

Substantial Utility

The Examiner asserts that the utility of being a diagnostic for melanoma and esophageal tumors is not a substantial utility because it "requires or constitutes carrying out further research to identify or reasonably confirm a 'real world' context of use." The Examiner discounts the data from Example 18 arguing that there is "no guidance in the specification as to how high the levels of overexpression are," and "no information in the specification as to the differences in expression or whether the results were statistically significant." Furthermore the Examiner asserts that Applicants "have provided no indication of the nature or number of samples that were used." According to the Examiner, "the declaration of Grimaldi does not teach the level of reproducibility or the level of reliability of the results." The Examiner asks "[i]f a clinician took a skin or esophageal tissue sample from a patient with suspected melanoma or esophageal cancer, what is the likelihood that when compared with normal tissue, the level of PRO3566 from the patient would be higher or lower ... [h]ow many samples would be needed ... [w]hat sensitivity would be needed?"

The Examiner argues that "[t]he only thing Applicants teach is that the gene was 'more highly expressed,' and this does not enable the skilled artisan to differentiate amongst expression levels in order to diagnose any diseases." The Examiner relies upon Chen *et al.* (Mol. Cell. Proteomics., 1.4:304-313, 2002) to contradict Applicants' position that generally those of skill in the art recognize a correlation between mRNA expression and protein expression.

The Examiner dismisses the data from Example 18, arguing that the data are insufficient to establish the utility of the claimed invention. Applicants point out that the same Examiner has taken the opposite position in a related application, No. 10/063,705, where she acknowledged utility for wild-type nucleic acid sequences encoding PRO3566, based on the data presented in Example 18. Thus, the Examiner has taken the position that the data in Example 18 are indeed sufficient to establish utility of the differentially expressed nucleic acids related to PRO3566, but that same data are insufficient in the present application. Applicants respectfully request that the Examiner reconsider the argument from the instant Office Action, taking into account her position in Application No. 10/067,705.

Applicants submit that the data in Example 18 are sufficient to establish the utility of the differentially expressed nucleic acids. It follows that the encoded PRO3566 polypeptides have utility because it is well-established in the art that a change in the level of mRNA for a particular protein generally leads to a corresponding change in the level of the encoded protein. In other words, if the encoding nucleic acid is differentially expressed, the generally accepted rule in the art is that the encoded polypeptide will also be differentially expressed.

A polypeptide that is differentially expressed in tumor cells compared to normal cells has utility. The PRO3566 polypeptide therefore has utility because, given the data in Example 18, one of skill in the art would recognize that the PRO3566 polypeptide is differentially expressed in melanoma and esophageal tumors.

Furthermore, Applicants point out that M.P.E.P. § 2107.01 III quotes *In re Brana*, 51 F.3d 1560, 1566, 34 U.S.P.Q.2d 1436 (Fed. Cir. 1995) in stating that "Usefulness in patent law ... necessarily includes the expectation of further research and development..." (emphasis added). Further, "to violate § 101 the claimed device must be totally incapable of achieving a

useful result." *Juicy Whip Inc. v. Orange Bang Inc.*, 51 U.S.P.Q.2d 1700 (Fed. Cir. 1999), *citing Brooktree Corp. v. Advanced Micro Devices, Inc.*, 977 F.2d 1555, 1571 (Fed. Cir. 1992).

Also, Applicants remind the Examiner that:

> A small degree of utility is sufficient . . . The claimed invention must only be capable of performing some beneficial function . . . An invention does not lack utility merely because the particular embodiment disclosed in the patent lacks perfection or performs crudely . . . A commercially successful product is not required . . . Nor is it essential that the invention accomplish all its intended functions . . . or operate under all conditions . . . partial success being sufficient to demonstrate patentable utility . . . In short, **the defense of non-utility cannot be sustained without proof of total incapacity**. If an invention is only partially successful in achieving a useful result, a rejection of the claimed invention as a whole based on a lack of utility is not appropriate. M.P.E.P. at 2107.01 (underline emphasis in original, bold emphasis added, citations omitted).

Here, with regard to the data in Example 18 and the differential expression of the PRO3566 polypeptide, the Examiner is requiring more than is necessary to satisfy the utility requirement. In particular, the Examiner is requiring excessive experimentation, precision and clinical development for the claimed subject matter. Applicants have proven that the claimed nucleic acids are differentially expressed in melanoma and esophageal tumor as compared to normal skin and esophagus tissue, and that therefore, it is more likely than not that the encoded polypeptides also are differentially expressed. This differential expression can be used to distinguish normal skin and esophagus tissue from melanoma and esophageal tumor. Use of the polypeptides or nucleic acids as diagnostics in every melanoma or esophageal tumor diagnosis is not required for utility. As long as the claimed polypeptides can be used as diagnostics in just one instance, *i.e.*, they are not totally incapable of working at all, then the utility standard under § 101 is met.

Thus, contrary to the argument presented by the Examiner, no additional guidance is required in order to meet the utility standard. Example 18 in the specification provides sufficient information for purposes of utility for PRO3566 nucleic acids, as well as the encoded polypeptides and their binding antibodies. It is not necessary to provide additional information regarding "how high the levels of overexpression are, the nature or number of samples that were used, or about the differences in expression or whether the results were statistically significant." As set forth in the previously submitted Declaration by Grimaldi, "[t]he precise levels of gene expression are irrelevant; what matters is that there is a relative difference in expression between

normal tissue and tumor tissue." (Paragraph 7). Since it is the relative level of expression between normal tissue and suspected cancerous tissue that is important, the precise level of expression in normal tissue is irrelevant. Likewise, there is no need for quantitative data to compare the level of expression in normal and tumor tissue. As Mr. Grimaldi states, "If a difference is detected, this indicates that the gene and its corresponding polypeptide and antibodies against the polypeptide are useful for diagnostic purposes, to screen samples to differentiate between normal and tumor."

Applicants submit that the declaration of Mr. Grimaldi is based on personal knowledge of the relevant facts at issue. Mr. Grimaldi is an expert in the field and conducted or supervised the experiments at issue. Applicants remind the Examiner that "[o]ffice personnel must accept an opinion from a qualified expert that is based upon relevant facts whose accuracy is not being questioned." PTO Utility Examination Guidelines (2001) (emphasis added). In addition, declarations relating to issues of fact should not be summarily dismissed as "opinions" without an adequate explanation of how the declaration fails to rebut the Examiner's position. *In re Alton* 76 F.3d 1168 (Fed. Cir. 1996).

Finally, as mentioned above, the Examiner also cites Chen *et al.* (hereafter "Chen") to support the assertion that polypeptide levels cannot be accurately predicted from mRNA levels. In Chen, the authors examined the relationship between mRNA levels and protein levels in 76 lung adenocarcinomas and 9 non-tumor lung samples. Chen examined the global relationship between mRNA and the corresponding protein abundance by calculating the average mRNA and protein level of all the samples for each gene or protein, and then looked for a correlation across different genes. However, this measurement of a correlation across genes is not relevant to Applicants' asserted utility. Chen also looked at the level of mRNA of 98 individual genes and their corresponding proteins across the samples. Chen reports that 21.4% (21 of 98) of the genes showed a statistically significant correlation between protein and mRNA expression.

Chen provides scant evidence to counter Applicants' asserted utility for the claimed antibodies because portions of Chen support Applicants' assertions, and the remaining portions provide little insight into the relationship between mRNA levels and corresponding protein levels for mRNA that is differentially expressed in tumor cells relative to normal cells. Rather than looking for mRNAs which were differentially expressed, Chen merely selected proteins whose

identity could be determined regardless of any changes in expression level (Chen at 306, right column). Importantly, it is not known if there was any substantial difference in mRNA levels for the various genes across samples – in short, with the exception of the genes in Figures 2A-2C, it is not known if the genes examined were differentially expressed. Also of significance for Applicants' asserted utility is the fact that Chen did not attempt to examine any differential expression between the cancerous lung samples and the non-cancerous lung samples – Chen did not distinguish between cancer and normal samples in their analysis.

Applicants have asserted that changes in mRNA levels, particularly those which are two-fold or greater, will correspond with measurable changes in polypeptide expression. The data in Chen support Applicants' assertion. In Figures 2A-2C, Chen plots mRNA value versus protein value for three genes. In these figures, a wide range of mRNA expression levels were observed (approximately seven- to eight-fold), and a correlation between mRNA and protein levels was observed for all three mRNA/protein pairs. This supports Applicants' asserted correlation between changes in mRNA levels which are two-fold or greater and changes in polypeptide expression.

The Examiner relies on the fact that Chen also reports a lack of correlation for some mRNA/protein pairs to support its assertion that polypeptide levels cannot be accurately predicted from mRNA levels. However, the lack of correlation reported by Chen could be a result of a lack of substantial changes in mRNA level. This can be understood by again turning to Figures 2A-2C. As noted above, where a wide range of mRNA expression levels are seen, a correlation between mRNA and protein levels was observed. However, if one examines the data points within a small range of mRNA levels for these same genes, *e.g.* 500-600 or 5000-6000 in Figs. 2A-2C, it is clear that a correlation would not be detected for the data within this range. This does not mean that a correlation between changes in mRNA and protein does not exist for these genes, as is evident when larger changes in mRNA expression are included in the analysis. Instead, this indicates that for relatively small changes in mRNA, any correlation is masked by imprecision in the measurements.

Chen's experiment compared mRNA levels versus protein levels across samples without selecting mRNA that showed a difference in expression level. And unlike Applicants, Chen did not examine differences in mRNA between tumor and normal tissue. Since almost all samples tested by Chen were from the same type of tissue, few substantial variations in the level of

mRNA or protein for a particular gene across the samples tested would be expected. Instead, it would be expected that most genes examined by Chen would have similar mRNA or protein levels across the samples. Figures 2A-2C of Chen demonstrate that the methods utilized by Chen cannot detect correlations between mRNA and protein levels when only small differences in mRNA expression are observed, but a correlation is detected when larger differences in mRNA expression are observed.

Accordingly, the only data reported by Chen which shows substantial changes in the expression of mRNA, Figures 2A-C, confirms Applicants' assertion that substantial changes in mRNA levels (*e.g.*, 2-fold or greater) will correspond to substantial changes in polypeptide expression. Further, this data also explains the lack of observed correlation between mRNA levels and protein levels for other genes reported by Chen. Thus, even given Chen's inability to detect a correlation between mRNA and protein in some genes, Chen's results do not refute Applicants' position.

Instead, Chen supports Applicants' position that a significant correlation between mRNA and protein levels exists for changes in mRNA levels that are 2-fold or greater. In further support of Applicants' position, Chen cites Celis *et al.* (FEBS Lett., 480:2-16 (2000)) stating that the authors "found a good correlation between transcript and protein levels among 40 well resolved, abundant proteins using a proteomic and microarray study of bladder cancer." *Chen* at 311, first column (emphasis added). As mentioned above, the lack of a correlation across genes is not relevant to Applicants' asserted utility, and therefore Chen's discussion of this issue and citation of Anderson and Seilhamer (Electrophoresis, 18:533-37 (1997)) and Gygi *et al.* (Mol. Cell. Bio., 19:1720-30 (1999)) offer no support for the PTO's position.

Even if the results in Chen supported the Examiner's argument, which they do not as discussed above, one contrary example does not establish that one of skill in the art would find it is more likely than not there is no general correlation between changes in mRNA level and changes in protein level for an individual gene. There are other non-transcriptional mechanisms for regulating gene and protein expression (*i.e.*, post-transcriptional regulation of genes, translation efficiency, etc.). However, as shown by the previously submitted argument, declarations of Grimaldi and Polakis, the scientific literature references, and textbooks, Applicants submit that the understanding in the art is that generally there is a correlation between a change in mRNA level and a change in protein level. In fact, the working hypothesis among

those skilled in the art, as illustrated by the evidence presented by Applicants, is that there is a positive correlation between changes in mRNA levels and changes in protein levels for a particular gene.

In conclusion, Applicants submit that the utility requirement under § 101 is satisfied because the PRO3566 polypeptide is differentially expressed in melanoma and esophageal tumors, and therefore, the claimed polypeptides are useful as diagnostic tools to distinguish tumor from normal tissue.

The Examiner has not offered any significant arguments or evidence to the contrary. Applicants have therefore established a utility for the claimed polypeptides as diagnostic tools for tumors, particularly melanoma and esophageal tumors.

Also, Applicants submit that the Examiner has failed to demonstrate that this is one of the "rare cases" where the applicants have "asserted a utility that could only be true if it violated a scientific principle, such as the second law of thermodynamics, or a law of nature, or was wholly inconsistent with contemporary knowledge in the art." M.P.E.P. § 2107.02 III B. In addition, Applicants submit that the Examiner has failed to meet its initial burden to offer evidence "that one of ordinary skill in the art would reasonably doubt the asserted utility." *In re Brana*, 51 F.3d 1560, 1566, 34 U.S.P.Q.2d 1436 (Fed. Cir. 1995).

Applicants submit that they have established that it is more likely than not that one of skill in the art would reasonably accept the utility for the claimed polypeptides as diagnostic tools as set forth in the specification. In view of the above, Applicants respectfully request that the Examiner reconsider and withdraw the utility rejection under 35 U.S.C. § 101.

Rejection under 35 U.S.C. §112, first paragraph – Enablement

The Examiner maintained the rejection of Claims 4-8 and 12-13 and also rejected new Claims 14-17 under 35 U.S.C. § 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to use the invention. The Examiner continues to argue that because the claimed invention is not supported by a substantial, specific and credible utility, the claims are not enabled.

Applicants submit that in the discussion of the 35 U.S.C. § 101 rejection above, Applicants have established a substantial, specific, and credible utility for the claimed

polypeptides. Applicants therefore request that the Examiner reconsider and withdraw the enablement rejection under 35 U.S.C. § 112, first paragraph, based on a lack of utility.

The Examiner also has maintained the rejection of Claims 4-5 and 12-13 for lack of enablement arguing that even if the specification were enabling for an isolated polypeptide of SEQ ID NO:64, it does not enable 95% or 99% variants of SEQ ID NO:64.

For Claims 4 and 5 the Examiner argues that being differentially expressed in melanomas or esophageal tumors is not a functional limitation, but is a characteristic of an individual sequence. The Examiner argues that one skilled in the art would not know how to make and use such differentially expressed sequences. Applicants respectfully disagree.

One of skill in the art would know how to make isolated polypeptides having at least 95% or 99% amino acid sequence identity to several polypeptides related to SEQ ID NO: 64. It is well-established in the art how to make polypeptides variants, including for example, variants which have at least 95% or 99% amino acid sequence identity to SEQ ID NO: 64.

Furthermore, the skilled artisan would know how to make isolated variants which satisfy the limitation "wherein said isolated polypeptide is more highly expressed in normal skin and esophageal tumor than in melanoma tumor and normal esophagus, respectively, or wherein said isolated polypeptide is encoded by a polynucleotide that is more highly expressed in normal skin and esophageal tumor than in melanoma tumor and normal esophagus, respectively." As previously discussed, the specification teaches how to determine if a molecule is differentially expressed in melanoma tumors or esophageal tumors compared to normal skin or normal esophagus, respectively.

Given that it is well known in the art to produce variant polypeptides, and that the specification teaches how to determine the expression pattern, Applicants submit that one of ordinary skill in the art would know how to make and use the sequences according to Claims 4-5 and 12-13.

Likewise, one of skill in the art would know how to make and use isolated polypeptides according to Claims 14-17. The Examiner argues that the limitation "wherein said isolated polypeptide or a fragment thereof can be used to generate an antibody which can be used to specifically detect the polypeptide of SEQ ID NO:64 in skin tissue or esophagus tissue samples"

is not a functional limitation. The Examiner argues that one of skill in the art would not know how to make a 95% or 99% variant peptide such that antibodies raised against it would recognize SEQ ID NO:64. Again, Applicants disagree.

One of skill in the art can easily make isolated polypeptides that are 95% or 99% identical to SEQ ID NO:64. Also, the specification teaches how to make antibodies to the polypeptide of SEQ ID NO: 64. These teachings can be used to generate antibodies against the variant sequences. Thus, one of skill in the art would know how to make and use the claimed polypeptides.

Given the skill in the art and the disclosure of how to make and use the claimed polypeptides, Applicants request that the Examiner reconsider and withdraw her rejection under 35 U.S.C. § 112, first paragraph.

Rejection under 35 U.S.C. §112, first paragraph – Written Description

The Examiner has maintained the rejection of Claims 4-5 and 12-13 under 35 U.S.C. §112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the art that the inventors, at the time the application was filed, had possession of the invention. The Examiner argues that the claims have no functional limitations. The Examiner further argues that the claimed sequences may have functions and structures which differ greatly from that of PRO3566.

Respectfully, Applicants assert that the instant patent application describes the invention in sufficient detail that one of skill in the relevant art could conclude that the inventor was in possession of the claimed variant sequences at the time the application was filed. The specification provides the entire sequence of the polypeptide of SEQ ID NO:64. It is well known in the art how to make polypeptides with at least 95% amino acid sequence identity to the sequence of SEQ ID NO:64. A sequence that is a 95% variant will differ from SEQ ID NO:64 by only about 16 amino acids. A 99% variant will differ from SEQ ID NO:64 by only 3-4 amino acids. Thus, the genus of polypeptides that have at least 95% or 99% amino acid sequence identity to the disclosed sequences will not have substantial variation. Therefore, one of skill in the art would recognize that Applicants possessed such variants at the time of filing the application.

Also, the specification discloses how to test to determine if the polypeptide is differentially expressed in skin tumors or esophageal tumors Further, one of skill in the art would further recognize possession of the claimed subject matter based upon the recitation in Claims 14 and 15 that the isolated polypeptide or a fragment thereof can be used to generate an antibody which can be used to specifically detect the polypeptide of SEQ ID NO:64 in skin tissue or esophagus tissue samples. In order for the variant sequence or fragment to generate an antibody that is cross reactive with SEQ ID NO:64, the variant or fragment will have structural similarity to SEQ ID NO:64. Those of skill in the art can easily make and test for such cross reactive antibodies, and produce variants that generate such antibodies.

In conclusion, Applicants submit that they have satisfied the written description requirement for the pending claims based on the actual reduction to practice of SEQ ID NO: 64, by specifying a high level of amino acid sequence identity, by describing how to test for differential expression of the polypeptide and encoding nucleic acid, and by describing how to make antibodies to the disclosed sequence, all of which result in a lack of substantial variability in the species falling within the scope of the instant claims. Applicants submit that this disclosure would allow one of skill in the art to "recognize that the applicant was in possession of the necessary common attributes or features of the elements possessed by the members of the genus." Hence, Applicants respectfully request that the Examiner reconsider and withdraw the written description rejection under 35 U.S.C. §112.

Rejection under 35 U.S.C. §102 – Anticipation

The Examiner maintained the rejection of Claims 4 and 5 as anticipated under 35 U.S.C. § 102 by Oka *et al.* (NCBI Accession No. BAA88132; published December 8, 1999) (hereinafter Oka), and by Janer *et al.* (NCBI Accession No. AC006163) (hereinafter Janer; submitted on December 8, 1998). Applicants respectfully traverse.

Oka et al.:

The Examiner has maintained the rejection of Claims 4 and 5 under 35 U.S.C. § 102(a) as being anticipated by Oka. The Examiner continues to state that Oka discloses an amino acid sequence that has 99% identity to SEQ ID NO: 64 of the instant invention, and therefore anticipates Claims 4-5, and previously submitted Claims 14-15. According to the Examiner, the

previously submitted Rule 131 declaration was ineffective to swear behind Oka because it was not signed by all of the inventors.

Attached herewith is the Declaration of Audrey Goddard, Paul J. Godowski, J. Christopher Grimaldi, Austin L. Gurney and William I. Wood under 37 C.F.R. §1.131 (referred to hereafter as "the Declaration of Goddard et al."), which establishes that the presently claimed invention antedates the publication date of Oka. The Declaration of Goddard et al. is signed by all of the inventors. It establishes that the presently claimed subject matter was conceived prior to the publication date of Oka, December 8, 1999, and diligently reduced to practice on a date after the submission date of Oka. Thus, Applicants respectfully submit that the cited reference is not available as prior art, and request that the rejections under 35 USC §102(a) be withdrawn.

As set forth in 37 C.F.R. § 1.131, a patent applicant "may submit an appropriate oath or declaration to establish invention of the subject matter of the rejected claim prior to the effective date of the reference or activity on which the rejection is based." *See also*, M.P.E.P. § 715. "The affidavit or declaration must state FACTS and produce such documentary evidence and exhibits in support thereof as are available to show conception and completion of the invention in this country ... at least conception being at a date prior to the effective date of the reference." *See* M.P.E.P. § 715.07 (emphasis in original). The showing of facts must be sufficient to show "conception of the invention prior to the effective date of the reference coupled with due diligence from prior to the reference date to a subsequent (actual) reduction to practice." *See id.*

Oka was published on December 8, 1999. The Declaration and attached Exhibit A demonstrate that the claimed subject matter, particularly a polypeptide having the sequence of SEQ ID NO: 64, was conceived by Applicants prior to December 8, 1999. Furthermore, as evidenced by the Declaration and Exhibit B, Applicants exhibited diligence in reducing the subject matter of the claims to practice from at least just prior to the submission date of Oka, by performing various assays to confirm the function of the polypeptide.

Therefore, Oka is not prior art under 102(a).

Janer et al.:

The Examiner also continues to reject Claim 4 as anticipated under 35 U.S.C. § 102(b) by Janer which was submitted on December 8, 1998. The Examiner states that the instant polypeptide claims are anticipated because Janer discloses a nucleic acid sequence which

encodes a polypeptide that is 98% identical to SEQ ID NO: 64 of the instant invention, and therefore anticipates Claim 4 and new Claim 14. Respectfully, Janer does not anticipate.

Janer does not anticipate Claims 4 and 14 because it does not disclose an isolated polypeptide. Janer only discloses a nucleic acid sequence. In fact, Janer discloses a sequence with more than 44,000 nucleotides, but it provides no information regarding any isolated polypeptide. Janer does not anticipate parts (a) and (b) of Claims 4 and 14 because Janer does not disclose an isolated polypeptide with identity to the amino acid sequence of SEQ ID NO:64, with or without its associated signal peptide.

Furthermore, Janer does not anticipate part (c) because it fails to disclose an isolated polypeptide. Janer does not disclose the amino acid sequence of the polypeptide encoded by the full-length coding sequence of the cDNA deposited under ATCC accession number 203650 for the following additional reasons. The Examiner argues that the nucleic acid sequence taught by Janer inherently encodes a polypeptide that is 98% identical to SEQ ID NO:64. Respectfully, Applicants disagree. The following sequence is a 1,431 nucleotide fragment out of the 44 kilobase nucleotide sequence of Janer. The fragment has some similarity to the nucleic acid sequence of SEQ ID NO:63.

caggatgcagggccgcgtggcagggagctgcgctcctctgggcctgctcctggtct
gtcttcatctcccaggtatggaggccgtgatgcccttgggcaggagggactggagg
tccccccaggaaacaggaattaaggaaaggggtaaaggcaggagggtacacatttag
gtccctgagggaaaaggaagaataggcataggggaagcaaagggaactggggactc
ggggactggagaccactggttgctttatcttccctttccctcaggcctctttgccc
ggagcatcggtgttgtggaggagaaagtttcccaaaacttggggaccaacttgcct
cagctcggacaaccttcctccactggcccctctaactctgaacatccgcagcccgc
tctggaccctaggtctaatgacttggcaagggttcctctgaagctcagcgtgcctc
catcagatggcttcccacctgcaggaggttctgcagtgcagaggtggcctccatcg
tgggggctgcctgccatggattcctggccccctgaggatccttggcagatgatggc
tgctgcggctgaggaccgcctgggggaagcgctgcctgaagaactctcttacctct
ccagtgctgcggccctcgctccgggcagtggcctttgcctggggagtcttctccc
gatgccacaggcctctcacccgaggcttcactcctccaccaggactcggagtccag
acgactgccccgttctaattcactgggagccgggggaaaaatcctttcccaacgcc
ctccctggtctctcatccacagggttctgcctgatcacccctggggtaccctgaat
cccagtgtgtcctggggaggtggaggccctgggactggttggggaacgaggcccat
gccacaccctgagggaatctggggtatcaataatcaaccccaggtaccagctggg
gaaatattaatcggtatccaggaggcagctggggaaatattaatcggtatccagga
ggcagctggggaatattaatcggtatccaggaggcagctggggaatattcatct
atacccaggtatcaataacccatttcctcctggagttctccgccctcctggctctt
cttggaacatcccagctggcttccctaatcctccaagccctaggttgcagtggggc
tagagcacgatagagggaaacccaacattgggagttagagtcctgctcccgccct
tgctgtgtgggctcaatccaggccctgttaacatgtttccagcactatccccactt

ttcagtgcctcccctgctcatctccaataaaataaaagcacttatggaatttgctt
ctccttggtttctttgtttctgggcataagctgaagtgagtctgggcataagctga
agtgagtctgttcattcctgttttctagcca

Lightly shaded sequence: Possible coding region of the Janer sequence.

Darker shaded sequence: Extra sequence of 197 nucleotides.

The fragment sequence begins at nucleotide 14,987 and ends at nucleotide 16,417. The following is the translation of the 1,431 base nucleotide sequence of Janer:

MQGRVAGSCAPLGLLLVCLHLPGMEAVMPLGRRDWRSPRKQELRKGVKAGGYTFR
SLREKEE*A*GKQRELGTRGLETTGCFIFPFPQASLPGASVLWRRKFPKTWGPTC
LSSDNLPPLAPLTLNIRSPLWTLGLMTWQGFL*SSACLHQMASHLQEVLQCRGGL
HRGGCLPWIPGPLRILGR*WLLRLRTAWGKRCLKNSLTSPVLRPSLRAVALCLGS
LLPMPQASHPRLHSSTRTRSPDDCPVLIHWEPGEKSFPNALPGLSSTGFCLITPG
VP*IPVCPGEVEALGLVGERGPCHTLRESGVSIINPQVPAGEILIGIQEAAGEIL
IGIQEAAGGILIGIQEAAGGIFIYTQVSITHFLLEFSALLALLGTSQLASLILQA
LGCSG

The encoded amino acid sequence has very little identity with the sequence of SEQ ID NO:64. Thus, Janer does not disclose the amino acid sequence of the polypeptide encoded by the full-length coding sequence of the cDNA deposited under ATCC accession number 203650.

Nonetheless, the Examiner continues to argue that the sequence of Janer inherently encodes a polypeptide according to Claim 4. Applicants disagree because the sequence of Janer does not "necessarily and always" encode a polypeptide according to the Claim 4. One difference between the nucleic acid sequence of Janer and the instant SEQ ID NO:63 is that the sequence of Janer includes an extra 197 nucleotides. It should be noted that the extra 197 nucleotides are located toward the 5' end of Janer fragment. The extra 197 nucleotides not only encode an amino acid sequence that is very different from the instant sequences, but also cause a frame shift for all codons that occur downstream. Thus, because the sequence of Janer has the 197 extra nucleotides, it encodes a very different polypeptide than the polypeptide of SEQ ID NO:64. The Examiner in arguing that the sequence of Janer inherently encodes a protein that is 98% identical to SEQ ID NO:64 ignores the 197 extra nucleotides and the amino acids encoded by those nucleotides. It should be understood that Janer provides no guidance or teaching regarding the removal of the 197 nucleotides. The 197 nucleotide sequence is not a consensus intron sequence. One of skill in the art looking at the sequence of Janer would not know to remove the 197 nucleotides, and would therefore recognize the sequence as encoding a protein

that is very different from the sequence of SEQ ID NO:64. Only with the benefit of impermissible hindsight using Applicants' sequence was the Examiner able to combine different fragments of Janer in order to reconstruct a nucleic sequence that would encode a polypeptide with some similarity to SEQ ID NO:64. Again, Janer does not teach or disclose such a constructed sequence. Thus, Janer does not inherently anticipate because it does not necessarily and always encode a polypeptide that meets the limitations of Claim 4.

For these reasons, Janer does not teach a 95% variant according to Claim 4 or Claim 14.

In view of the above, Applicants respectfully request reconsideration and withdrawal of the rejections under 35 U.S.C. §102.

CONCLUSION

In view of the above, Applicants respectfully maintain that claims are patentable and request that they be passed to issue. Applicants invite the Examiner to call the undersigned if any remaining issues may be resolved by telephone.

Please charge any additional fees, including any fees for additional extension of time, or credit overpayment to Deposit Account No. 11-1410.

Respectfully submitted,

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Dated: August 15, 2005

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